With respect to the preparation of the compounds of the present invention, the Examiner has indicated that Applicants have improperly incorporated essential material by reference. Applicants wish to rely on Japanese (Kokai) 62-286949. Accordingly, Applicants have amended page 24, line 23 of the specification to provide a detailed discussion of preparation of the compounds of the present invention. In addition, as requested by the Examiner, Applicants have now provided a declaration by the Applicants' undersigned representative confirming that no new matter has been added by this amendment to the specification.

Claims 1-41 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. There were nine different issues raised by the Examiner. Each be addressed in the order set forth in the Official Action.

The Examiner has pointed out that claims 1, 14, 16, 29, 30 and 38-41 recite "carboxyl group which is optionally esterified or amidated." Applicants believe that this terminology is sufficiently clear to allow one of ordinary skill in the art to practice the claimed invention. The modification of the carboxyl group is only the carboxyl group which is set forth on the R_4 substituent. That position is at the far right end of compound (I). One of ordinary skill in the art would have sufficient knowledge and understanding to determine the extent of the esterification and amidation in order to maintain the desirable properties of the claimed compound. It would not require undue experimentation for one of ordinary skill in the art to make such a determination. Accordingly, Applicants do not believe that an amendment of the claims is necessary. Should the Examiner wish to discuss

this further, a telephone call to Applicants' undersigned representative would be appreciated.

On issue b, the Examiner has noted that Applicants recite several phenyl groups for variable Z. The Examiner has requested that the groups be separated by commas. Applicants wish to point out that it is not typical to place commas between each of the chemical formulas because the commas would not be readily understood and may be misinterpreted. Accordingly, Applicants have not amended the claims by inserting commas between chemical formulas as requested by the Examiner. Each of the groups are clearly meant to be alternatives and are not intended to be linked to each other. If linkage was desired, there would be an actual linkage suggested either by a solid line or dotted lines.

With respect to issue c, Applicants have amended claims 10-13 to recite method claims and therefore the Examiner's comments with respect to the preamble are no longer relevant.

With respect to issue d, the Examiner has indicated claim 20 is an improper multiple dependent claim. Applicants wish to point out that they amended claim 20 on page 2 of the Preliminary Amendment filed November 18, 1999. Therefore, claim 20 is not a multiple dependent claim.

With respect to issue e, once again, Applicants have amended claims 14, 29 and 30 to convert them to method claims and therefore a discussion of preamble is relevant.

With respect to issue f, likewise, Applicants have amended claims 25-28 to recite method claims and the discussion of the preamble is no longer on point.

With respect to issue g, the Examiner has pointed out that claims 38 and 39 appear to be substantial duplicates. Applicants, nevertheless wish to retain claims 38 and 39 since claim 38 relates to the inhibition of NF-κB. Claim 39 more specifically recites the treatment of diseases caused by activation of NF-κB. There may be times where it is desirable to inhibit NF-κB production even if a recognized disease state was not present. Treatment modalities and treatment protocols vary significantly and Applicants wish to retain both claims 38 and 39 since it would be preferable to maintain both sets of claims in order to better enforce the invention at a later date.

With respect to issue h, Applicants wish to maintain both claims 40 and 41 for the same reasons as maintained in claims 38 and 39.

With respect to issue i, the Applicant has indicated that the phrase "benzoquinone derivative" appears to be unclear. In particular, the Examiner said the cite where formula I can be derived into another compound does not appear to be clear. Applicants wish to point out that they used the phrase "benzoquinone derivative" only to better describe compound (I). Since the benzoquinone portion of formula (I) is clear, it is a convenient shorthand abbreviation way of characterizing compound (I). The fact that the word "derivative" was used is simply to mean that the formula of compound (I) is not solely or simply a benzoquinone but that other substituents can and will be present. In particular, such substitutions on the benzoquinone ring are clearly set forth and characterized as R_1, R_2, R_3, R_4, Z and n. The terminology that Applicants have selected is very commonly used in the art.

Claims 14, 29 and 38-41 have been rejected under 35 U.S.C. §112, first paragraph, because the invention is allegedly not enabled for the prevention of diseases related to NF-κB and TNF-α using the compounds of formula I. Applicants respectfully traverse this rejection.

The Examiner has not challenged the treatment aspect of Applicants invention but rather the prevention aspect. Once again, Applicants wish to point out that often times the prevention as well as the treatment of particular disease state or condition are one and the same. For instance, once a patient is treated for a particular disease state, Applicants may maintain the same dosage or a comparable dosage of medication in order to prevent the reoccurrence of that disease state of condition. Many disease states go into remission and treatment may or may not be continued in order to delay or prevent the onset of further symptoms. This is very typical, especially with many of the disease states which can be treated by the present invention.

Accordingly, Applicants maintain that their invention correctly covers both the prevention as well as the treatment of a variety of disease states and conditions.

The Examiner has also mentioned the incorporation by reference for essential material. As indicated earlier the Applicants have amended their specification as requested by the Examiner.

Accordingly, the rejection of claims 14, 29, and 38-41 under 35 U.S.C. §112, first paragraph, should be withdrawn.

Applicants note that there are three art rejections of record. Claims 1-14, 16-34 and 37 have been rejected under 35 U.S.C. §102(a)/(b) as being anticipated by Suzuki et al. In

addition, claims 1-34 and 37 have been rejected under 35 U.S.C. §102(a)/(b) as being anticipated by Tatsuoka and Suzuki et al. Finally, claims 1-34 and 37 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Tatsuoka and Suzuki et al.

In order to expedite prosecution on the merits, Applicants have amended all of their compound and composition of matter claims to convert them into method of use or method of treatment claims. There is no suggestion or disclosure in any of the references of record to use Applicants' compounds for the inhibition of NF-κB or the treatment or prevention of diseases caused by the activity of NF-κB nor is there any suggestion or motivation provided by any of the references for the inhibition of TNF-α production nor the prevention or treatment of disease states caused by excessive TNF-α production.

Accordingly, Applicants believe that the claims presently of record are free of all prior art.

In view of the foregoing, Applicants believe that the subject application is now in condition for allowance. Should the Examiner have any questions or helpful suggestions, a telephone call to Applicants undersigned representative would be appreciated.

Respectfully submitted,
BURNS, DOANE, SWECKER & MATHIS, L.L.P.

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Teresa Stanek Rea
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Date: July 12, 2001

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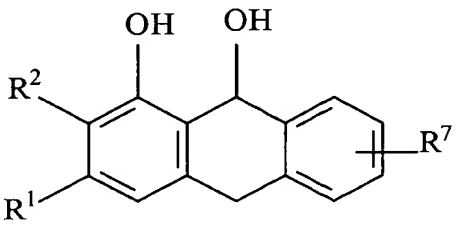
Page 24, Paragraph Beginning at Line 18

The benzoquinone derivative of the general formula (1) that is used as an active ingredient of the present invention may be prepared according to the method described in Japanese Unexamined Patent Publication (Kokai) No. 62 (1987)-286949 or Chem. Pharm. Bull., 44(1): 139-144 (1996) or a method based thereupon. The compound represented by the general formula (I) of Japanese Unexamined Patent Publication No. 62-286949 can be produced, for example, by the following methods:

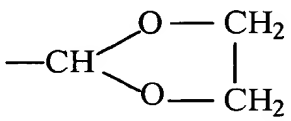
Process I

A compound represented by the general formula (IV)



(IV)

(wherein R^1, R^2 and R^3 each independently represents a hydrogen atom, a methyl group or a methoxy group, and R^7 represents a group



or $-CH(OC_2H_5)_2$)

can be obtained by acting a halide Grignard reagent represented by a general formula (III)

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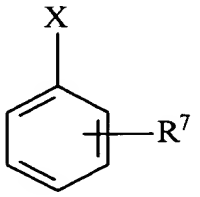
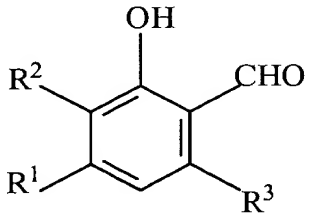


(III)

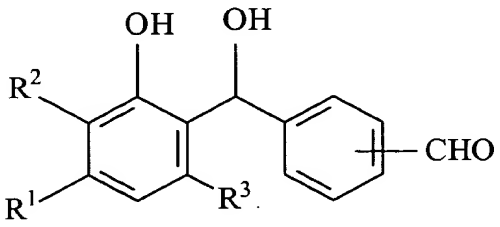
(wherein X represents a bromine atom or a chlorine atom and R^7 is as define above)

to an aldehyde represented by a general formula (II)



(II)

(wherein R^1, R^2, and R^3 are as defined above). The compound (IV) is converted into an aldehyde represented by a general formula (v)



(V)

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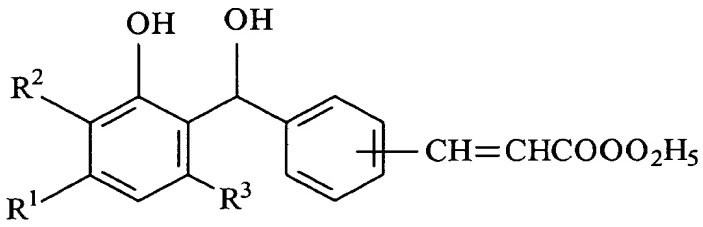
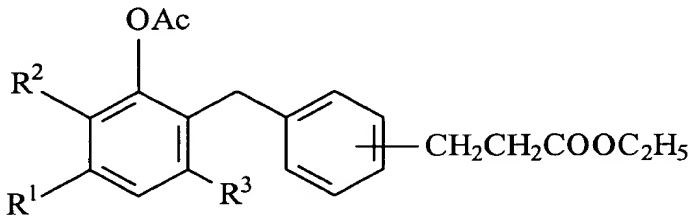
an acid, for example, hydrochloric acid. A compound represented by a general formula (VI)



(VI)

(wherein R^1, R^2, and R^3 are as defined above) can be obtained by acting Witting reagent of triethylphosphonoacetate to the aldehyde.

The compound (VI) is converted into an acetylated compound by reacting thereto, acetic anhydride in the presence of a base, for example, pyridine, and, subsequently, the acetylated compound is catalytically reduced in the presence of palladium black in glacial acetic acid to obtain a compound represented by a general formula (VII)



(VII)

(wherein R^1, R^2, and R^3 are as defined above).

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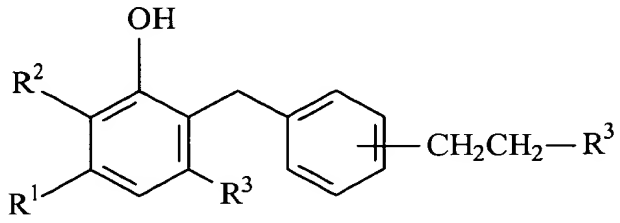
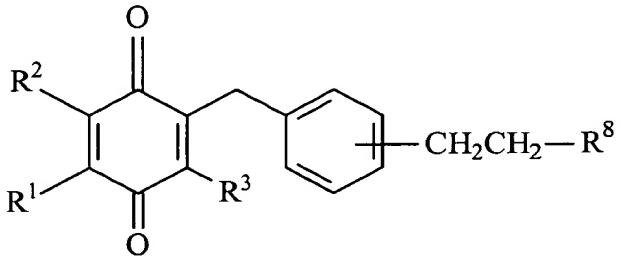
The compound (VII) is subjected to hydrolysis, reduction or esterification through a conventional method to obtain a compound represented by a general formula (VIII)



(VIII)

(wherein R^1, R^2, and R^3 are as defined above and R^8 represents a hydroxymethyl group, a carboxyl group, or a lower alkoxycarbonyl group).

Subsequently, the compound (VIII) is oxidized with oxygen in the presence of potassium nitrosodisulfonate or salcomine, to obtain the compound of the present invention of the general formula (Ia)



(Ia)

(wherein R^1, R^2, and R^3 are as defined above).

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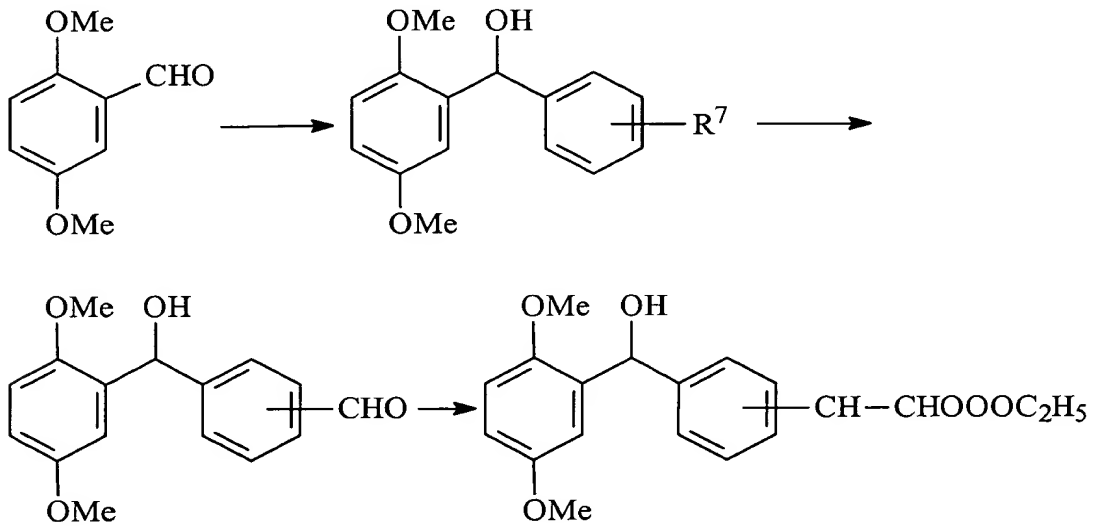
The compound of the present invention may be also produced by the following method:

Process II

A compound of a general formula (IX) can be obtained from 2,5-dimethoxybenzaldehyde through the following route as described above.



(IX)

The compound (IX) is converted into a chloride using thionychloride, etc. and, then, is subjected to dechlorination, for example reduction with zinc-glacial acetic acid to obtain a compound of a formula (X).

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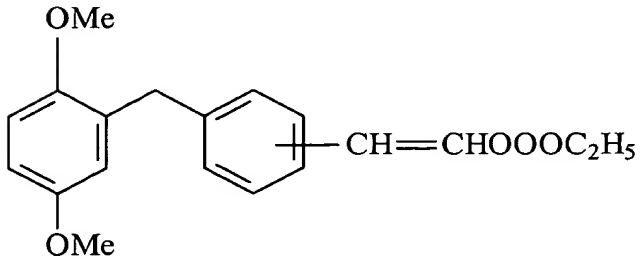
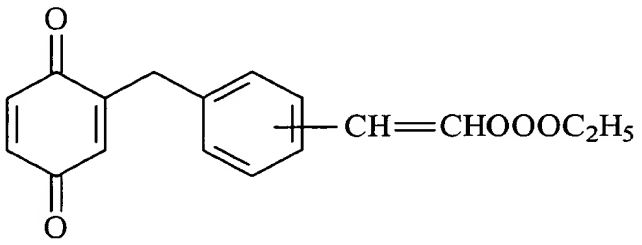


(X)

The compound represented by a formula (Ib) of the present invention can be obtained by oxidation of the compound (X) with ammonium nitrate cesium (hereinafter abbreviated to CAN).



(Ib)

The compound (Ib) may be converted into various compounds of the present invention through hydrolysis, reduction, amidation, etc., as appropriate, under conventionally employed condition.

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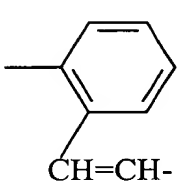
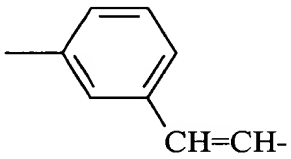
Marked-up Claims 2-13, 15, 17-28 and 38-41

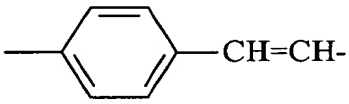
2. (Thrice Amended) The [NF-κB inhibitor composition] method according to claim [1] 38 wherein R_1 and R_2 are a hydrogen atom, a methyl group, or a methoxy group.

3. (Thrice Amended) The [NF-κB inhibitor composition] method according to claim [1] 38 wherein R_3 is a hydrogen atom or a methyl group.

4. (Thrice Amended) The [NF-κB inhibitor composition] method according to claim [1] 38 wherein Z is







and n is an integer 0.

5. (Thrice Amended) The [NF-κB inhibitor composition] method according to claim [1] 38 wherein Z is

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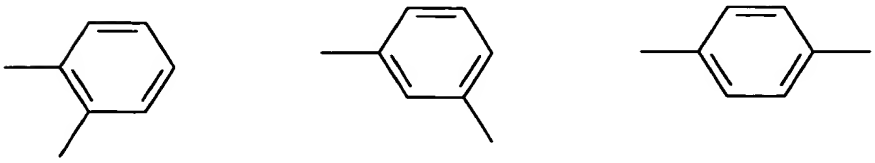
Marked-up Claims 2-13, 15, 17-28 and 38-41



and n is an integer 1, 2, or 3.

6. (Thrice Amended) The [NF-κB inhibitor composition] method according to claim [1] 38 wherein R_4 is a group -$COOR_5$ wherein R_5 is a hydrogen atom, an optionally substituted alkyl group having 1 to 8 carbons, an optionally substituted phenyl group, or an optionally substituted aralkyl group having 7 to 11 carbons.

7. (Thrice Amended) The [NF-κB inhibitor composition] method according to claim [1] 38 wherein R_4 is a group -$CONR_6R_7$ wherein R_6 and R_7 are each independently a hydrogen atom, an optionally substituted alkyl group having 1 to 8 carbons, an optionally substituted bicyclic unsaturated or partially saturated hydrocarbon ring group having 9 to 11 carbons, an optionally substituted heterocyclic group, an optionally substituted phenyl group, an optionally substituted aralkyl group having 7 to 11 carbons, or a heteroaryl-C_1-C_3-alkyl group, or R_6 and R_7, together with the nitrogen atom to which they are attached, represent a heterocyclic group which may further contain a nitrogen, oxygen, and/or sulfur atom.

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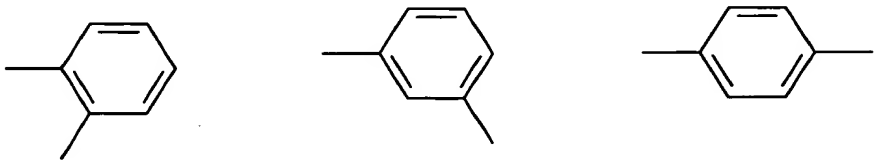
Marked-up Claims 2-13, 15, 17-28 and 38-41

8. (Thrice Amended) The [NF-κB inhibitor composition] method according to claim [1] 38 wherein R_4 is a group -$CONR_6R_7$ wherein R_6 and R_7, together with the nitrogen atom to which they are attached, represent a 5- to 10-membered optionally substituted, nitrogen-containing heterocyclic group which may contain, in addition to the carbon and nitrogen atom, 1 to 3 heteroatoms selected from the group consisting of a nitrogen, oxygen and sulfur atom, the carbon atom on said cyclic group being optionally a ketone form or the sulfur atom on said cyclic group being optionally an oxide form.

9. (Thrice Amended) The [NF-κB inhibitor composition] method according to claim [1] 38 wherein R_1 and R_2 are a methyl group or a methoxy group; R_3 is a methyl group: R_4 is a carboxyl group which is optionally esterified or amidated; Z is



and n is an integer 1, 2, or 3.

10. (Thrice Amended) The [NF-κB inhibitor composition] method according to claim [1] 38 wherein the suppressing agent for the gene expression of one or more

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Marked-up Claims 2-13, 15, 17-28 and 38-41

substances is selected from the group consisting of IL-1, TNF-α, IL-2, IL-6, IL-8, iNOS, granulocyte colony-stimulating factor, inteferon-β, ICAM-1, VCAM-1, ELAM-1, major histocompatibility system class I, major histocompatibility system class II, β2-microglobulin, immunoglobulin light chain, serum amyloid A, angiotensinogen, complement B, complement C4, c-myc, HIV, HTLV-1, SV40, CMV, and adenovirus.

11. (Thrice Amended) The [NF-κB inhibitor composition] method according to claim [1] 38 which is a [preventive or therapeutic agent] prophylactic or treatment for inflammatory diseases.

12. (Thrice Amended) The [NF-κB inhibitor composition] method according to claim [1] 38 which is a [preventive or therapeutic agent] prophylactic or treatment for autoimmune diseases.

13. (Twice Amended) The [NF-κB inhibitor] method according to claim [1] 38 which is a [preventive or therapeutic agent] prophylactic or treatment for viral diseases.

15. (Amended) [A novel] The method according to claim 38 wherein the compound is selected from:

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Marked-up Claims 2-13, 15, 17-28 and 38-41

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]morpholine,

N-[3-(4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]thiomorpholine S-oxide,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4- benzoquinon-2-ylmethyl)phenyl]propionyl]thiomorpholine S-dioxide,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]piperidine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]dimethylamine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]isopropylamine,

N-(3-(4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]ethanolamine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]benzylamine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]phenethylamine,

N-[3-(4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]acryloyl]morpholine,

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Marked-up Claims 2-13, 15, 17-28 and 38-41

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]acryloyl]thiomorpholine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]acryloyl]piperidine,

N-[3-(4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]acryloyl]dimethylamine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]acryloyl]isopropylamine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]acryloyl]ethanolamine,

N-[3-[4-(5,6-,dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]acryloyl]benzylamine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]acryloyl]phenethylamine,

N-[3-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]piperidine,

N-[3-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]pronionyl]thiomorpholine,

N-[3-[3-(5,6-di-methoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]morpholine,

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Marked-up Claims 2-13, 15, 17-28 and 38-41

N-[3-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]isopropylamine,

3-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]acrylic acid,

N-[3-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]acryloyl]piperidine,

N-[3-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]acryloyl]morpholine,

N-[3-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]acryloyl]isopropylamine,

N-[3-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]acryloyl]thiomorpholine,

N-[3-[4-(3,5,6-trimethyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]isopropylamine,

N-[3-[4-(3,5,6-trimethyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]piperidine,

N-[3-(4-(3,5,6-trimethyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]morpholine,

N-[3-[3-(3,5,6-trimethyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]isopropylamine,

N-[3-[3-(3,5,6-trimethyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]piperidine,

3-[2-(5,6-dimethoxy-3-methyl-1,4-benzoquino-n-2-ylmethyl)phenyl]acrylic acid,

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Marked-up Claims 2-13, 15, 17-28 and 38-41

N-[3-[2-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]acryloyl]thiomorpholine,

3-[2-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionic acid,

N-[3-[2-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]piperidine,

N-[3-[2-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]morpholine,

N-[3-[2-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]thiomorpholine,

N-[3-[2-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]isopropylamine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-(s)-2-(methoxymethyl)pyrrolidine,

N-[3-(4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]isonipecotamide,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-4-methylpiperidine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-2-methylpiperidine,

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Marked-up Claims 2-13, 15, 17-28 and 38-41

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-3-methylpiperidine,

N-[3-(4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-4-methoxyaniline,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-2-hydroxyaniline,

N-(3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-3,4-dimethoxyaniline,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-D,L-alaninol,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-D,L-pipecolic acid ethylester,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-L-prolinamide,

4-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoqui-non-2-ylmethyl)phenyl]propionyl] aminophenylacetonitrile,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-4-pentylaniline,

N-[3-(4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-(s)-(-)-l-phenylethylamine,

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N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-(R)-(+)-l-phenylethylamine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-1,3-dimethylbutylamine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]cycloheptylamine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-3,5-dimethylpiperidine,

1-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon72-ylmethyl)phenyl]propionyl]-4-ethoxycarbonylpiperazine,

1-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-4-phenylpiperazine,

1-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-4-hydroxy-4-phenylpiperidine,

1-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-4-(4-chlorophenyl)-4-hydroxypiperidine,

1-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-4-(2-methoxyphenyl)piperazine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline,

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4-acetyl-4-phenyl-l-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]piperidine,

N-(3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-1,2,3,4-tetrahydroisoquinoline,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]isoamylamine,

N-[3-[4-(5,6-dimethoxy-3-methyl-1,4- benzoquinon-2-ylmethyl)phenyl]propionyl]cyclohexylamine,

N-(3-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]propionyl]-4-hydroxyaniline,

4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)benzoic acid,

N-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)benzoyl]morpholine,

N-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)benzoyl]isopropylamine,

N-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)benzoyl]piperidine,

N-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)benzoyl]thiomorpholine,

3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)benzoic acid,

N-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)benzoyl]isopropylamine,

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N-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)piperidine,

N-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)morpholine,

N-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)thiomorpholine,

4-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]-n-butyric acid,

N-[4-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]butanoyl]morpholine,

N-[4-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]butanoyl]thiomorpholine,

N-[4-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]butanoyl]piperidine,

N-(4-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]butanoyl]isopropylamine,

4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenylacetic acid,

N-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenylacetyl]morpholine,

N-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenylacetyl]piperidine,

N-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenylacetyl]thiomorpholine,

N-[4-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenylacetyl]isopropylamine,

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3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenylacetic acid,

N-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenylacetyl]piperidine,

N-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenylacetyl]thiomorpholine,

N-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenylacetyl]morpholine,

N-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenylacetyl]morpholine,

4-(3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]-n-butyric acid,

N-[4-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]butanoyl]piperidine,

N-(4-[3-(5,6-dimetho--y-3-methyl-1,4-benzoquin on-2-ylmethyl)phenyl]butanoyl]thiomorpholine,

N-[4-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]butanoyl]morpholine, and

N-[4-[3-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-ylmethyl)phenyl]butanoyl]isopropylamine.

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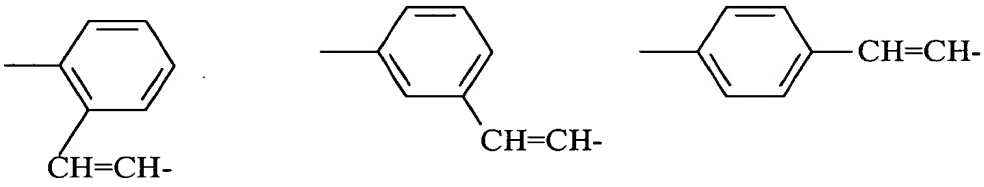
17. (Thrice Amended) The [TNF-α production inhibitor composition] method according to claim [16] 40 wherein R_1 and R_2 are a hydrogen atom, a methyl group, or a methoxy group.

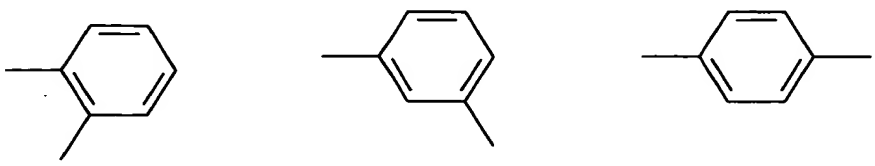
18. (Thrice Amended) The [TNF-α production inhibitor composition] method according to claim [16] 40 wherein R_3 is a hydrogen atom or a methyl group.

19. (Thrice Amended) The [TNF-α production inhibitor composition] method according to claim [16] 40 wherein Z is



and n is an integer 0.

20. (Thrice Amended) The [TNF-α production inhibitor composition] method according to claim [16] 40 wherein Z is



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and n is an integer 1, 2, or 3.

21. (Thrice Amended) The [TNF-α production inhibitor composition] method according to claim [16] 40 wherein R_4 is a group -$COOR_5$ wherein R_5 is a hydrogen atom, an optionally substituted alkyl group having 1 to 8 carbons, an optionally substituted phenyl group, or an optionally substituted aralkyl group having 7 to 11 carbons.

22. (Thrice Amended) The [TNF-α production inhibitor composition] method according to claim [16] wherein R_4 is a group -$CONR_6R_7$ wherein R_6 and R_7 are each independently a hydrogen atom, an optionally substituted alkyl group having 1 to 8 carbons, an optionally substituted bicyclic unsaturated or partially saturated hydrocarbon ring group having 9 to 11 carbons, an optionally substituted heterocyclic group, an optionally substituted phenyl group, an optionally substituted aralkyl group having 7 to 11 carbons, or a heteroaryl-C_1-C_3-alkyl group, or R_6 and R_7, together with the nitrogen atom to which they are attached, represent a heterocyclic group which may further contain a nitrogen, oxygen, and/or sulfur atom.

23. (Thrice Amended) The [TNF-α production inhibitor composition] method according to claim [16] 40 wherein R_4 is a group -$CONR_6R_7$ wherein R_6 and R_7, together with the nitrogen atom to which they are attached, represent a 5- to 10-membered

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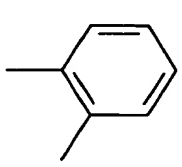
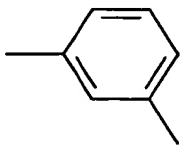
optionally substituted, nitrogen-containing heterocyclic group which may contain, in addition to the carbon and nitrogen atom, 1 to 3 heteroatoms selected from the group consisting of a nitrogen, oxygen and sulfur atom, the carbon atom on said cyclic group being optionally a ketone form or the sulfur atom on said cyclic group being optionally an oxide form.

24. (Thrice Amended) The [TNF-α production inhibitor composition] method according to claim [16] 40 wherein R_1 and R_2 are a methyl group or a methoxy group; R_3 is a methyl group: R_4 is a carboxyl group which is optionally esterified or amidated; Z is


and n is an integer 1, 2, or 3.

25. (Thrice Amended) The [TNF-α production inhibitor composition] method according to claim [16] 40 wherein the suppressing agent for the gene expression of one or more substances is selected from the group consisting of IL-1 TNF-α, IL-2, IL-6, IL-8, iNOS, granulocyte colony-stimulating factor, inteferon-β, ICAM-1, VCAM-1, ELAM-1,

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plasminogen activator-inhibiting factor I, major histocompatibility system class I, major histocompatibility system class II, β2-microglobulin, immunoglobulin light chain, serum amyloid A, angiotensinogen, complement B, complement C4, c-myc, HIV, HTLV-1, SV40, CMV, and adenovirus.

26. (Thrice Amended) The [TNF-α production inhibitor composition] method according to claim [16] 40 which is a [preventive or therapeutic agent] prophylactic or treatment for inflammatory diseases.

27. (Thrice Amended) The [TNF-α production inhibitor composition] method according to claim [16] 40 which is a [preventive or therapeutic agent] prophylactic or treatment for autoimmune diseases.

28. (Thrice Amended) The [TNF-α production inhibitor composition] method according to claim [16] 40 which is a [preventive or therapeutic agent] prophylactic or treatment for viral diseases.

38. (Amended) A method for inhibiting NF-κB comprising administering to a patient in need of NF-κB inhibition a benzoquinone derivative represented by the following general formula (1):

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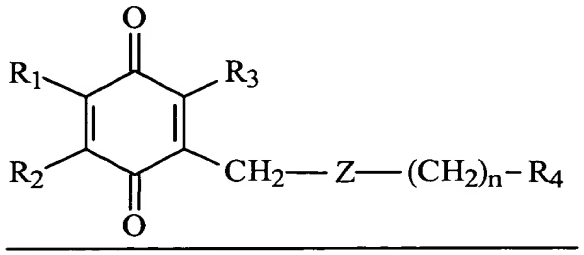
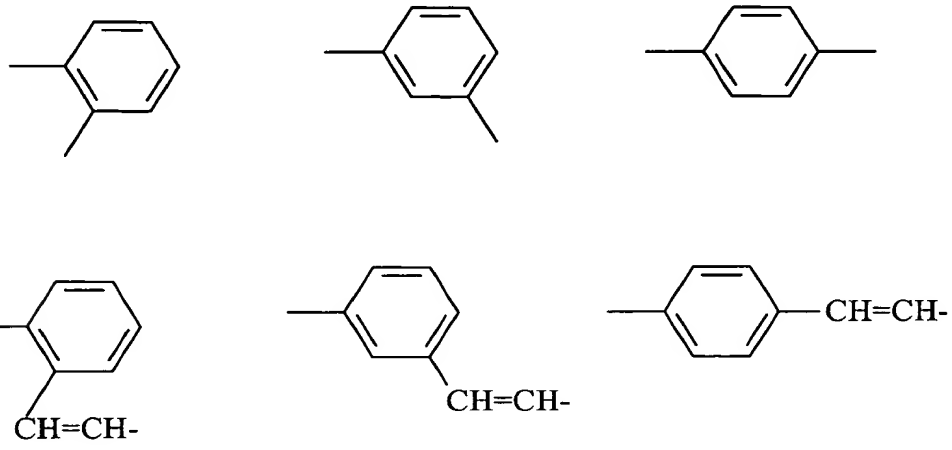


wherein

R_1, R_2 and R_3 are each independently a hydrogen atom, an alkyl group having 1 to 5 carbons, or an alkoxy group having 1 to 5 carbons;

R_4 is a hydrogen atom, a hydroxymethyl group, an alkyl group, or a carboxyl group which is optionally esterified or amidated;

Z is



and, n is an integer from 0 to 6, or its hydroquinone form, or a pharmaceutically acceptable salt thereof.

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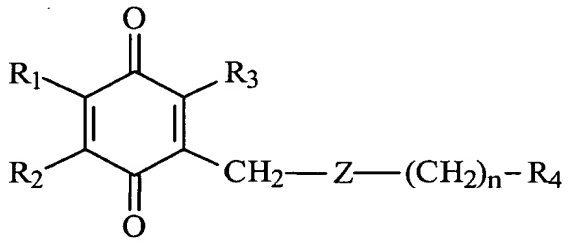
39. (Amended) A method for preventing or treating diseases caused by the activation of NF-κB comprising administering to a patient a benzoquinone derivative represented by the following general formula (1):

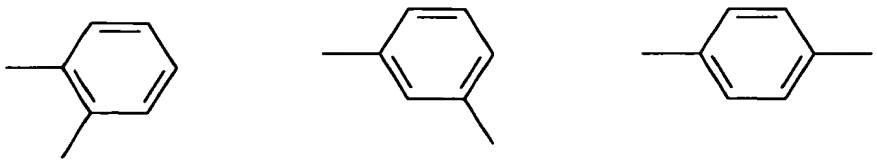


wherein

R_1, R_2, and R_3 are each independently a hydrogen atom, an alkyl group having 1 to 5 carbons, or an alkoxy group having 1 to 5 carbons;

R_4 is a hydrogen atom, a hydroxymethyl group, an alkyl group, or a carboxyl group which is optionally esterified or amidated;

Z is



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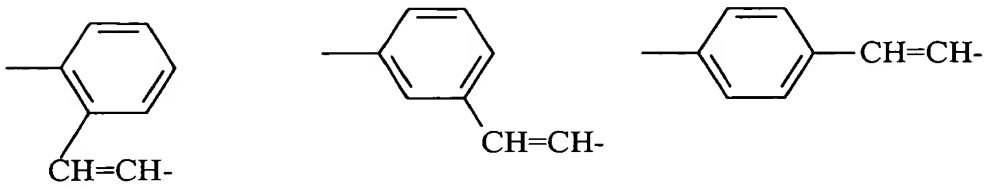
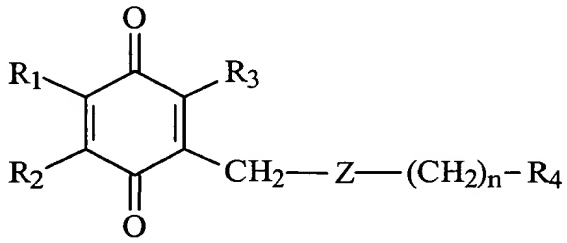


and, n is an integer from 0 to 6,

or its hydroquinone form, or a pharmaceutically acceptable salt thereof.

40. (Amended) A method for inhibiting TNF-α production comprising administering to a patient in need of TNF-α inhibition a benzoquinone derivative represented by the following general formula (1):



wherein R_1, R_2 and R_3 are each independently a hydrogen atom, an alkyl group having 1 to 5 carbons, or an alkoxy group having 1 to 5 carbons;

R_4 is a hydrogen atom, a hydroxymethyl group, an alkyl group, or a carboxyl group which is optionally esterified or amidated;

Z is

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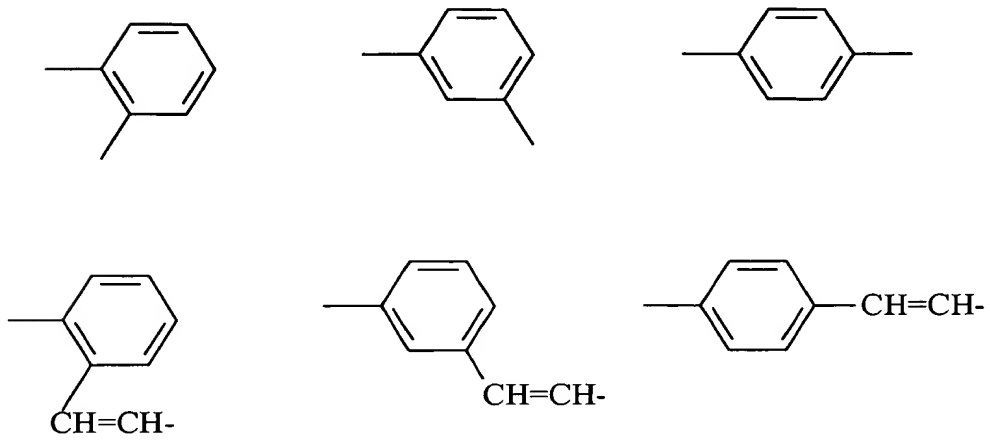
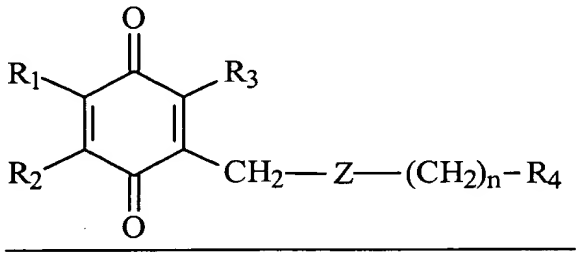


and, n is an integer from 0 to 6,

or its hydroquinone form, or a pharmaceutically acceptable salt thereof.

41. (Amended) A method for preventing or treating diseases caused by the excessive production of TNF-α comprising administering to a patient a benzoquinone derivative represented by the following general formula (1):



wherein R_1, R_2 and R_3 are each independently a hydrogen atom, an alkyl group having 1 to 5 carbons, or an alkoxy group having 1 to 5 carbons;

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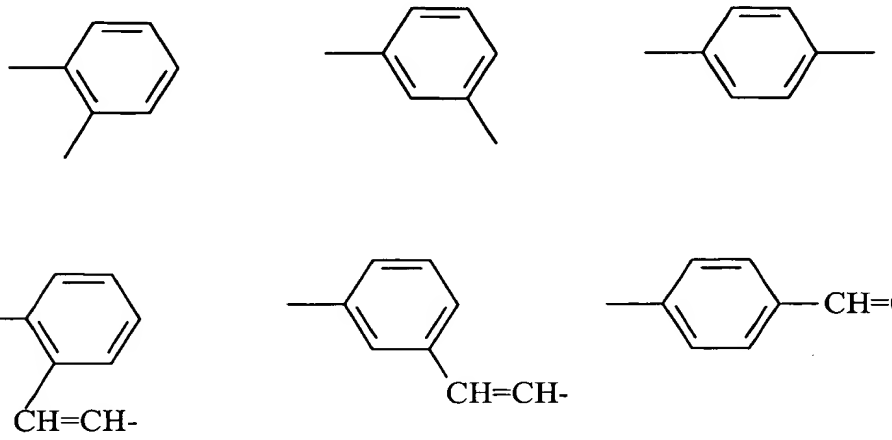
R_4 is a hydrogen atom, a hydroxymethyl group, an alkyl group, or a carboxyl group which is optionally esterified or amidated;

Z is



and, n is an integer from 0 to 6,

or its hydroquinone form, or a pharmaceutically acceptable salt thereof.